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LI, QIAN JANICE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,747	BLAU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-13,19-21,34,39 and 41-50* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 3, 8-13, 19-21, 34, 39, 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/5/07 has been entered.

The amendment, declaration, and remarks filed 11/5/07 are acknowledged. Claims 1, 14-18, 22, 23, 35-38, 40 have been canceled. Claims 2-13, 19-21, 34, 39 have been amended, and claims 41-50 are newly submitted. The claims are subject to a species election.

Election/Restrictions

Applicant's election with traverse of species drawn to G-CSF as the mobilizing agent, NGF as the neuronal factor, and treating neurodegenerative disorders, is acknowledged. The traversal is on the ground(s) that applicant claiming the genus in the broad sense, not specific species, and restriction would "unjustifiably limit the scope of independent claims that have not been examined on merits". This is not found persuasive. MPEP states, " WHERE AN APPLICATION INCLUDES CLAIMS DIRECTED TO DIFFERENT EMBODIMENTS OR SPECIES THAT COULD FALL WITHIN THE SCOPE OF A GENERIC CLAIM, RESTRICTION

BETWEEN THE SPECIES MAY BE PROPER IF THE SPECIES ARE INDEPENDENT OR DISTINCT" (MPEP 806.04). Instant claims encompasses multitude of species, each drawn to treating a distinctive disease with a unique combination of cytokines and neuronal factors; the diseases have different etiology, and pathogenesis, would require different treatment strategy and different fields of search. The different cytokines and neural factors have different chemical structures and biological effects on different disease conditions, belong to different chemical entities, would require different fields of search. It would impose a severe search burden on the Office if all of the species are examined together. The examination of the elected species does not limit the scope of the claimed invention because the species is a representative of the genus, the generic claims are examined at least to the extent they are represented by the elected species. If any of the criteria for patentability under 35 USC was not met for the species, the generic claims would not have been patentable. Further, the Office has clearly indicated in the restriction requirement, the claims shall be restricted only if no generic claims found to be allowable; and Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141.

Further, the Office has clearly requested should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly

admit on the record that this is the case. The applicant fails to provide such evidence on record.

The applicant then argues that claims 4-7 recite different limitations on the cells of claim 34, and do not intrinsically contain the subject matter of non-elected group I.

The arguments have been fully considered but found not persuasive. Because claim 34 is directed to "administering an agent that mobilizes bone marrow cells to an individual having a neuron deficiency", hence, the bone marrow cells being mobilized could only be those from the individual (autologous). The elected invention does not involve administering bone marrow cells as do the non-elected groups I, II. Moreover, the specification fails to teach administering said agent to one individual would mobilize bone marrow cells from another individual (allogeneic), thus the limitations of claims 4-7 would make sense in group I or II, but not the elected group III.

M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate search fields. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final

action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 2-13, 19-21, 34, 39, 41-50 are pending, however, claims 4-7, 46-50 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to teach an agent that mobilizes bone marrow cells also "induces" formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual as now claimed. The subject matter is now considered to be new matter.

MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE

APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. In the instant case, the specification as originally filed describes that transplanted bone marrow cells are capable of crossing blood-brain barrier and contribute to neuronal cells, particularly purkinje neurons (e.g. Specification, Examples 3-4). However, the specification is completely silent on any agent that is capable of inducing formation of the Purkinje/BM-derived heterokaryon as now claimed. The applicant indicated that support for amended and new claims could be found in line 4 of page 38, and pages 50-54. However, page 37-38 teaches using G-CSF for bone marrow mobilization, not for inducing formation of fusion between Purkinje neuron and bone marrow cells. Page 50-54 discuss the results of bone marrow cell transplantation following lethal irradiation, not the result of administering G-CSF. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed. Accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed 11/5/07 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

To the extent that the claimed subject matter are not described in the instant disclosure, claims 2, 3, 8-13, 19-21, 34, 39, 41-45 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The amended claims recite "a method for producing a Purkinje/bone marrow-derived heterokaryon, comprising: administering an agent that mobilizes bone marrow cells to *an individual having a neuron deficiency*". Given the broadest reasonable interpretation in light of the specification, the intended use of the method is for therapy of a neuron deficiency, and hence instant claims still embrace a therapeutic method drawn to treating a neuronal deficiency by administering a bone marrow cell mobilization therapy, and will be evaluated by the standard.

The specification reviews the types of neuronal deficiency that could be treated by the instantly claimed invention, which include almost every known neurological disease, ranging from congenital neural deficiency to Parkinson's. The specification teaches that the inventors found that bone marrow-derived cells are capable of entering the nervous system and forming bone marrow derived neurons, particularly Purkinje neurons, and then contemplates using such approach for regeneration of neurons and treating neuronal disorders. The specification prophetically states that these diseases could be treated with a bone marrow cell mobilization treatment (paragraph 0089), and refers to prior art for details of the treatment citing *Chao et al*, (Blood, 1993), who administered G-CSF to "mobilize" macrophages and platelets for promoting bone marrow recovery from high dose chemotherapy. However, *Chao et al* use G-CSF in a completely different circumstance for achieving different goals, where patients underwent chemotherapy and administering growth factor G-CSF promoted regeneration of new blood cells. *Chao* reference does not provide any teaching regarding treating a neuronal disease/symptom, and thus cannot substitute a specific

guidance for practicing instantly claimed invention for forming Purkinje neuron or treating neuronal deficiency. The specification fails to provide any evidence that administering G-CSF, or any agent to that matter, would induce the formation of new Purkinje neuron in the nerve system, the specification fails to provide any evidence there are new formation of Purkinje neuron/BMC heterokaryon brought about by administering G-CSF. The specification only provided evidence that tail vein administering bone marrow cells following lethal irradiation lead to formation of Purkinje/BMC heterokaryon. Although the instant specification provides preliminary studies on migration, relocation, and contribution of transplanted BMDCs to Purkinje neurons in the brain, it fails to teach whether administering G-CSF would boost relocation of bone marrow cells to the brain, and induce their differentiation into neurons. The specification fails to teach the efficacy of such BM mobilization processes, whether it is sufficient to the extent that any clinical benefit could be observed. The specification also fails to provide any evidence that administering G-CSF ameliorates any one symptom of any one neuronal deficiency, and thus fails to provide an enabling disclosure for what is now claimed.

The statue under 35 U.S.C 112, first paragraph requires "THE SPECIFICATION SHALL CONTAIN A WRITTEN DESCRIPTION OF THE INVENTION, AND OF THE MANNER AND PROCESS OF MAKING AND USING IT, **IN SUCH FULL, CLEAR, CONCISE, AND EXACT TERMS** AS TO ENABLE ANY PERSON SKILLED IN THE ART TO WHICH IT PERTAINS, OR WITH WHICH IT IS MOST NEARLY CONNECTED, TO MAKE AND USE THE SAME AND SHALL SET FORTH THE BEST MODE CONTEMPLATED BY THE INVENTOR OF CARRYING OUT HIS INVENTION" (emphasis added). "**IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED**

MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING". In the instant case, using bone marrow cell mobilization therapy to treat neuronal deficiency is a novel idea presented by instant applicant, little is known in the art about how to make this idea feasible, and the state of the art is such that years after instant priority date, there is no known means that is sufficient for treating neuronal deficiency, and hence it is upon the applicant to provide an enabling disclosure to guide the practice of instantly claimed invention at the time of instant filing date. The MPEP states, "**THERE MAY BE TIMES WHEN THE WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE A REASONABLE DOUBT AS TO THE ACCURACY OF A PARTICULAR BROAD STATEMENT PUT FORWARD AS ENABLING SUPPORT FOR A CLAIM.** THIS WILL ESPECIALLY BE THE CASE WHERE THE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES. MOST OFTEN, ADDITIONAL FACTORS, SUCH AS THE TEACHINGS IN PERTINENT REFERENCES, WILL BE AVAILABLE TO SUBSTANTIATE ANY DOUBTS THAT THE ASSERTED SCOPE OF OBJECTIVE ENABLEMENT IS IN FACT COMMENSURATE WITH THE SCOPE OF PROTECTION SOUGHT AND TO SUPPORT ANY DEMANDS BASED THEREON FOR PROOF. [FOOTNOTE OMITTED.] (MPEP 2164.02, 03).

Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must

> supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to describe any specific agent or condition under which and using such agent the bone marrow cell mobilization therapy can be carried out to assert neurological benefit, and it fails to teach what kind of effect in the brain tissue one is to expect upon the stem cell mobilization. Although the specification briefly mentioned bone mobilization therapy was known in the art, the art use such therapy for a completely different purpose. Hence there is a failure to meet the enablement requirement.

Although it had become known at around time of instant filing that bone marrow cells have the potential to differentiate into neuronal cells (*Kopen et al*, PNAS 1999;96:10711-6; *Sanchez-Ramos et al*, Exp Neurol 2000;164;247-56; *Mezey et al*, Science 2000;290:1779-82), which has the potential for neuron regeneration, the state of the art was in the infant stage of development. The bone marrow mobilization treatment was not considered equal to the bone marrow transplantation, and the BMT was far from treating any neuronal diseases. The inefficiency of new neuron formation, and the unknown function of the bone marrow-differentiated cells that bear neuron surface markers, among others, are a few of the reasons that art needs further development to reach the level of therapeutic use. The specification fails to address the aforementioned art-known hurdles, and it fails to provide an enabling disclosure to support what is now claimed.

The amended claims also contemplate combined use of neural factors with G-CSF and other bone marrow mobilization agent. To this end, the state of the art is such that *in vitro* or animal model study showing promising therapeutic effect of neuronal factors often cannot be translated to clinical benefit. *Garcia* (Neurotox Res 2000;2:115-37) teaches,

> Neurotrophic factors are compounds that enhance neuronal survival and differentiation. Most of these compounds exert their pharmacological actions on selective types of neurons, and therefore, are considered promising new therapeutic agents for the treatment of different neurodegenerative disorders characterized by selective degeneration of certain neuronal groups. Those compounds have been used in humans for several neurological disorders including amyotrophic lateral sclerosis--ciliary derived neurotrophic factor (CNTF) and brain derived neurotrophic factor (BDNF), Alzheimer's disease and peripheral neuropathy--nerve growth factor (NGF) and Parkinson's disease (PD)--glial derived neurotrophic factor (GDNF). In spite of well founded clinical experiments by previous experimental work in animal models some of these trials have been negative. For instance, animal models of PD have shown that several neurotrophic factors, including GDNF and other compounds, reduce apoptosis and increase resistance of dopamine neurons to neurotoxins in vitro. These compounds prevent or recover the damage to dopamine neurons of rodents and primates produced by chemical or mechanical acute lesions including 6-OH-DA, MPTP, methamphetamine and axotomy. The differences between the promising results obtained in experimental models and the lack of clinical results or excessive toxicity found in humans could be attributed to the following reasons: (a) Lack of relevance between the pathogenesis of the experimental lesion and the corresponding neurodegenerative disorder. (b) Poor correlation between results obtained in acute, self-limited, selective deficit produced to experimental animals and those available in more complex, chronic and progressive disorders involving patients. (c) Inadequate delivery of the active product to the target area in the human brain. (d) Poor information from acute experiments in animals which does not predict long-term effects of chronic infusion in humans. Further experimental work, therefore, is needed to transfer these neurotrophic factors to the clinic. (Emphasis added)

Larkfors (J Neurochem 1996;66:1362-73) teaches, that Purkinje neuron fails to respond to the treatment of NGF (e.g. the abstract).

The specification fails to provide evidence contrary to the observation of *Larkfors* and *Garcia*, and the specification is completely silent with regard to addressing or

overcoming the art known hurdles, and hence, the prophetic teaching of the specification fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Response to Arguments

Applicant's arguments filed 11/5/07 have been fully considered but they are not persuasive for reasons following:

The applicant first cited the case law for *in vitro* and *in vivo* correlation, and asserting all that is required to enable instant claims are a reasonable correlation between the animal model and the human disease.

In response, at issue for instant non-enablement is not whether an animal model or an *in vitro* condition correlates with human disease, but lacking any showing in an animal model or an *in vitro* study establishing a bone marrow mobilization agent caused the migration of the recipient bone marrow cells to the brain, and induced the formation of Purkinje/BMC as now claimed.

Further, from the teaching of the skilled as taught by *Garcia*, the state of the art is such in the context of neuronal degenerative disease model and human disease, there was a lack of relevance between the pathogenesis of the experimental lesion and corresponding neurodegenerative disorder; there was poor correlation between results obtained in acute, self-limited, selective deficit produced to experimental animals and

those available in more complex, chronic and progressive disorders involving patients, and there was inadequate delivery of the active product to the target area in the human brain, and there was poor information from acute experiments in animals which does not predict long-term effects of chronic infusion in humans. In view of such state of the art, and the disclosure provided by the applicant, instant claims remain in the purview of speculation.

Applicant then asserts since claims have been amended no longer to recite treating a neuron deficiency, and there is no need to demonstrate any therapeutic effect.

In response, the claims are evaluated given the broadest reasonable interpretation consistent with the teaching of the specification. As such, the intended use of instantly claimed invention still is therapeutic, and thus proper to be evaluated by the standard. Now, the questions to be asked in the context of enablement are two-fold, i.e. whether administering G-CSF to an individual suffering a neurodegenerative disorder could induce formation of Purkinje/BMC heterokaryon, and if so, whether the produced heterokaryon is sufficient to bring about a clinical benefit, and the specification fails to address both questions as discussed *supra*, and thus it fails to provide an enabling disclosure.

The applicant then cited numerous prior art of record supporting the assertion that "administering an agent that mobilizes bone marrow cells can serve as a substitute for injection of bone marrow cells", and "since the applicant already demonstrated that injected bone marrow cells can nevigate the blood circulation and find their way to the

CNS, there is no scientific reason to doubt that mobilized bone marrow cells cannot do the same". The relevance of each reference is addressed following:

Zohlnhofer (JAMA 2006): reporting G-CSF stem cell mobilization in patients with acute myocardial infarction. *Zohlnhofer* teaches the study was initiated based on experimental studies and early phase clinical trials suggesting bone marrow derived stem cells may improve cardiac regeneration after acute myocardial infarction, and concluded "*Stem cell mobilization by G-CSF therapy in patiens with acute myocardial infarction and successful mechanical reperfusion has no influence on infarct size, left ventricular function, or coronary restenosis*" (e.g. the abstract).

Bodine (Blood 1994): reporting G-CSF mobilized peripheral cells has been shown to participate in hematopoietic recovery. They examined the accessibility of the mobilized cells to genetic manipulation, and suggested it is an alternative to bone marrow cells for gene therapy protocols. Bondine does not teach mobilization therapy and neuronal regeneration.

Orlic (PNAS 2001): reporting mobilized bone marrow cells repair the infarcted heart, improving function and survival in animal models. However, *Zohlnhofer,* published after Orlic, establishes that this exciting treatment strategy does not work in humans.

Durhsen (Blood 1988): reporting G-CSF significantly increased circulating stem cells in cancer patients. G-CSF treatment is beneficial for preparing donors of bone marrow cells, but not substitution for BMT.

Lane (Blood 1995): reporting G-CSF treatment is beneficial for preparing donors of bone marrow cells, but not substitution for BMT.

Lemoli (Blood 1997): reporting G-CSF treatment is beneficial for preparing donors of bone marrow cells, but not substitution for BMT.

Sudo (Blood 1997): reporting synergistic effect of Flt-3L with G-CSF treatment for preparing transplantation donors of bone marrow cells, but not substitution for BMT.

Leterveer (Blood 1996): reporting using IL-8 treatment for mobilizing bone marrow cells, but not substitution for BMT.

In summary, it is noted the two references using G-CSF mobilization for regeneration of another organ (heart) were published after instant filing date, and establish the method has no benefit on myocardial regeneration in humans.

The remain references report G-CSF effect on circulating progenitor cells for obtaining high quality donor cells for transplantation, not for substituting bone marrow cells with the G-CSF mobilization therapy. Hence, these references do not particularly support the applicant's assertion. From the numerous art cited, there is yet one reference clearly set forth that G-CSF substitutes for direct injection of bone marrow cells as asserted by the applicant. To the contrary, the needs to prepare donor for BMT implicitly suggest G-CSF has not replaced the need of bone marrow transplantation.

Applicant submitted declaration illustrating that the progeny of a single HSC can form heterokaryons with Purkinje neurons. The declaration clarifies the fact that no lethal irradiation is required for grafted bone marrow cells to navigate to the brain.

However, this showing does not address that it is G-CSF that induces the formation of Purkinje/bone marrow-derived heterokaryon.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

It is noted the following art rejection applied because of the applicant's assertion, "since the applicant already demonstrateed that injected bone marrow cells can nevigate the blood circulation and find their way to the CNS, there is no scientific reason to doubt that mobilized bone marrow cells cannot do the same".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 3, 21, 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by *Rudolf et al.* (J Neural Transm 1997;104:1305-1311).

Instant claims are directed to a method comprising the step of administering G-CSF to an individual having a neurodegenerative disease.

Rudolf teaches administering G-CSF to a patient suffering Parkinson's disease (neurodegenerative disorder, see e.g. page 1306). Accordingly, *Rudolf* anticipates instant claims.

Note claims 39, 41-44 describe an intrinsic effect upon administering G-CSF, and hence even though this and other references do not teach the effect, it would occur upon administering G-CSF to a subject.

Claims 2, 3, 21, 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by *Squadrido et al.* (Brit J Pharmacol 1997;1:120:333-9).

Squadrido teaches administering G-CSF to rats having vascular dysfunction and ischemic-reperfusion injury (neuron deficiency involving "disorders of the spinal cord and vertebral column"), and reports increased survival rates in a dose-dependent manner, (see e.g. table 1, figure 1). Accordingly, *Squadrido* anticipates instant claims.

Claims 2, 3, 21, 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by *McManus et al.* (Int J Radia Oncol Biol Phys 1993;26:845-50).

McManus teaches subcutaneous administering G-CSF to patients having primary intracranial tumors (neuron deficiency involving "increased intracranial pressure") during radiation therapy, and reports G-CSF is a safe and effective treatment for neutropenia induced by extended radiotherapy (see e.g. the abstract and figures). Accordingly, *McManus* anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-13, 19, 20, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Squadrido et al.* (Brit J Pharmacol 1997;1:120:333-9), in view of *Culmsee et al.* (Eur J Pharmacol 1999;379:33-45).

Squadrido teaches administering G-CSF to rats having ischemic-reperfusion injury, which damaged nerve system of the individual, and reports increased survival rates in a dose-dependent manner, (see e.g. table 1, figure 1). *Squadrido* does not teach combining the G-CSF treatment with a neuronal factor.

Culmsee supplemented *Squadrido* by establishing it was well known in the art, neuronal factors, such as NGF plays a role in protecting neuron cells after ischemic brain injury. *Culmsee* teaches upon induced brain ischemic damage, NGF mRNA levels increased (e.g. figs 1-3), and concludes "THE RESULTS SUGGEST THAT GROWTH FACTOR SYNTHESIS IS ENHANCED IN ACTIVATED ASTROCYTES AND THAT THIS COULD BE THE MECHANISM OF CLENBUTEROL-INDUCED CEREBROPROTECTION AFTER ISCHEMIA" (see e.g. the abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Squadrido*, by including a nerve growth factor in the treatment as taught by *Culmsee* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit for neuron protection. As to the means and timing of administering of the two agents, they fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 2, 3, 19-21, 34, 39, 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al.* (WO 99/56759), in view of *Bodine et al.* (Blood 1994;84:1482-91, IDS) and *Eglitis et al.* (USP 7,022,321).

Sanchez-Ramos teaches bone marrow cells are source of neurons for brain and spinal cord repair. *Sanchez-Ramos* transplanted bone marrow cells into rat brain at striatum, wherein the bone marrow cells did not remain localized to the site of the graft, but migrate throughout the brain and integrated into specific brain regions. *Sanchez-Ramos et al* teaches the most orderly integration of bone marrow cells was in the laminar distribution of cerebella Purkinje cells, where the bone marrow derived cells took on the Purkinje neuron phenotype (see e.g. the abstract, examples 2, 7, 8). *Sanchez-Ramos* does not teach using bone marrow mobilization in place of bone marrow cell transplantation.

Bodine supplements *Sanchez-Ramos* by establishing that bone marrow cell mobilization therapies were widely practiced in the art at the time of the instant priority date, and it was widely known that such therapies result in the movement of bone marrow cells from the bone marrow into the circulation (as asserted by the applicant). *Bodine* found that G-CSF increased peripheral blood pluripotent stem cells by three fold in normal rats and 250-fold in splenectomized rats. *Bodine* reviews the state of the art has seen the capability of mobilized stem cells in hemotopoietic recovery, and suggest that mobilized peripheral progenitor cells may be the alternative to bone marrow cells in clinical therapy (e.g. column 2, page 1482).

Eglitis supplements *Sanchez-Ramos* in view of *Bodine* by establishing it was known in the art that intravenous injection of bone marrow progenitor cells would cross blood-brain barrier to arrive in the brain (e.g. the abstract, and example 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Sanchez-Ramos*, by using G-CSF mobilization in place of bone marrow transplantation as taught by *Bodine* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the mobilization therapy does not require a bone marrow donor and the transplantation procedure. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al.* (WO 99/56759), in view of *Bodine et al.* (Blood 1994;84:1482-91, IDS) and *Eglitis et al.* (USP 7,022,321), as applied to claims 2, 3, 19-21, 34, 39, 41-45 above, further in view of *Garcia* (Neurotox Res 2000;2:115-37).

The combined teaching *supra* does not teach combining the G-CSF mobilization with a neuronal factor.

Garcia supplemented the deficiency by establishing it was well known in the art, neuronal factors, such as NGF, have been used in treating neural degenerative disorder such as Parkinson's disease.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Sanchez-Ramos,* in view of *Bodine* and *Eglitis*, by including a nerve growth factor as taught by *Garcia* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit for neuron protection. As to the means and timing of administering of the two agents, they fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7:30 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

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QJL
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